Catecholamines

A Product of Clinical and Basic Science

IN THIS ISSUE OF CALIFORNIA MEDICINE we read that the basic scientist and clinician have developed a deep understanding of the pharmacologic features, synthesis and metabolism of catecholamines. As the scientist and clinician have applied their knowledge to medical practice, focus has once again been drawn to what may be called a recurrent cycle of interdependence between them. The value of this cycle is great and is apparently expected and certainly rewarded by the public which supports us. However, the threads which bind together the segments of medical science and practice are vulnerable. Indeed many in the profession wonder if they exist. This editorial proposes to further an awareness of the cycle and indicate its value to both the scientist and clinician. Only as we become aware and appreciative of the cycle will we conscientiously foster its continuance through frequent and intellectually stimulating contacts. These contacts, I believe, advance the standards of medical practice and the maintenance of scientific productivity. An analysis of the history of obtaining and using data related to catecholamines illustrates the cycle well, and fosters an appreciation of it.

If norepinephrine and epinephrine had little effect in man, would we have learned so much about the details of their pharmacologic effects? Without knowledge of the cardiovascular effects of catecholamines, would the pathogenesis of diseases like pheochromocytoma, Riley-Day or Zetterson's syndrome have been linked to abnormalities of catecholamine synthesis or metabolism? If such abnormalities had not attracted clinicians, would we have pressed for, provided, or even considered, funding for the investigations which led to a further realization of the pharmacologic potential of catecholamines?

We have learned that catecholamines affect many systems in addition to the cardiovascular. In part, the symptoms seen in patients with diseases characterized by excess production of or unusual sensitivity to catecholamines have justified and stimulated research on the pharmacologic properties of catecholamines. For instance, once we knew that catecholamines were present in selected areas of the brain, that drugs which altered the content or turnover of catecholamines altered mood, sleep, or behavior, and that patients with pheochromocytoma had mental aberrations and paresthesias, we had justification to question whether systematic administration of catecholamines, their precursors, metabolites or congeners could mimic selected neurologic diseases or possibly cure them.

After neurophysiologists had indicated the function of the basal ganglia and chemists had indicated their unique content of dopamine, and after dopamine concentration was found diminished in the basal ganglia of patients with Parkinson's disease, the stage was set for a series of experiments which revealed one of the most dramatic pharmacologic ameliorations ever known to neurologic disease. Medical investigators reasoned that because primary amines did not freely cross the blood brain barrier, dopamine administration would have little chance of replenishing the dopamine content of the basal ganglia. They chose the amino acid dopa because biochemists had indicated that L-amino acids were actively transported into brain, and L-amino acid decarboxylase was present in the central nervous system where the drug must be converted to dopa-

Studies on which these observations are based have been supported by NIH grants HL-09964, GM-01791 and GM-16496, and an NIH Special Fellowship, 1F03 HL-50244.

mine. Even with this knowledge, the first groups to administer dopa found no effect in patients with Parkinson's disease. Had it not been for well-documented principles of drug administration, formulated by pharmacologists and clinical pharmacologists, perhaps Cotzias would not have been so courageous and persistent in administering large doses of drug for long periods. The successful treatment was further refined after clinicians noted side effects of long-term administration of dopa that may have been due to the peripheral rather than central effects of dopamine. Pharmacologists were able to propose that drugs which block the peripheral but not the central nervous system decarboxylase activity could be useful in (a) limiting conversion of dopa to dopamine in peripheral tissues (therefore limiting the "peripheral" toxicity of any dose of dopa, and (b) allowing lower than ordinary doses to produce a given central effect, since a greater percentage of any given dose would be transported into the brain when the peripheral decarboxylase was inhibited.

The pharmacologists' proposals have been clinically realized. Furthermore, it is quite likely that the principle illustrated by these experiments will be applied to other therapeutic settings. In general, it will not be surprising to find that amino acid drugs which work centrally can be given in lower doses and with fewer side effects when their distribution to the brain is enhanced by a peripheral decarboxylase inhibitor. There is no serendipity here—rather, these are the results of forethought facilitated by communication.

The clinician may also establish where available knowledge is insufficient to explain certain symptoms of a complex attributed to excessive catecholamines. Because we have studied the pharmacologic properties of catecholamines, we know that the diarrhea associated with neuroblastoma or ganglioneuroma, the abnormalities of serum calcium, the appearance of flushing and hypotension, and the variation of symptom complexes in patients with pheochromocytoma cannot be explained by simple increases in catecholamines in the plasma. Thus, the clinician forces the scientist to return to his bench and, by this maneuver, the clinician has opened new areas of endeavor and understanding. His curiosity has propelled the scientist toward the evidence that tumors may be pluripotential, that there is a molecular relationship between catecholamines and insulin release and effect, or between catecholamines and gonadal or renal function. From the data in the symposium on catecholamines, the clinician may encourage the scientist further and may even say, "Thank you for demonstrating that alpha-mimetic amines inhibit insulin release, but help me to explain why, when alpha-adrenergic blocking agents reverse the abnormal insulin response in patients with pheochromocytoma, the glucose tolerance is still abnormal."

As the scientist returns to his bench and tubes, he could and should indicate that he cannot yet answer that question but he can issue some caveats. Since he has elucidated a profound effect of catecholamines on the physiologic response to glucose, vasopressin, and gonadal hormones, he might warn that serious disruption of physiology may occur while a patient is being treated for his obesity with amphetamines or with catecholamines in general. In addition, since betamimetic catecholamines may seriously alter the function of human leukocytes (not described in the symposium), the scientist may legitimately ask that the clinician observe carefully the patient receiving catecholamines during the course of an infection or inflammatory disease for evidence of specific effects of the drug that might be attributed to its newly found action on leukocytes. So the cycle continues, with potential benefit to all participants.

We should note the application of knowledge concerning the synthesis and metabolism of catecholamines. Aside from the obvious advantage of having stimulated intellectual efforts which resulted in at least two Nobel prizes in recent years, without this information clinicians might still be treating essential hypertension with rice diets, surgical sympathectomy or, at best, toxic ganglionic blocking drugs or Rauwolfia alkaloids. Instead, drugs that can competitively or noncompetitively antagonize the pharmacologic effects of catecholamines have been developed and have helped both in the diagnosis of diseases of catecholamine excess and assessment of the relative contribution of epinephrine and norepinephrine to a variety of diseases and physiologic states. The same drugs also contribute to the therapy of those diseases they help to discover.

Without a knowledge of metabolism we would have been unable to diagnose unequivocally pheochromocytoma with simple chemical techniques, and would also have been unable to design drugs

to interfere selectively with the function of the autonomic neurons and ganglia. Knowing the fine details of synthesis has allowed us to pinpoint rate-limiting steps in the formation of catecholamines and to design competitive inhibitors of critical enzymes (tyrosine hydroxylase and dopamine beta oxidase) that can lead to true decreases in the rate of catecholamine synthesis. These drugs (for example, alpha methyltyrosine) have been extraordinarily useful in selected instances of pathologic overproduction of catecholamines. Very likely, with the help of organic chemists and molecular pharmacologists, we will be able to design safer drugs, with great tissue specificity, that can be used to alter the modulating role of catecholamines on such diverse functions as glucose tolerance, hunger and obesity, sleep and inflammation.

The scientist may offer additional discoveries in the future. What will be the pragmatic importance of understanding more of the chemistry of the granules of the postganglionic nerve ending? Will there be clinical uses of medical sympathectomy, for example, with 6-hydroxy dopamine (not covered in the symposium)? If the past is any indication of the future, the clinicians will put such information to good use. Maybe they will also ask the scientist if stimulation of the gut by catecholamines will raise its cyclic adenosine 3′, 5′-monophosphate (AMP) content, as does cholera enterotoxin that causes the severest of diarrheas.

The example of applying basic facts concerning catecholamines to medical settings is not at all unique, nor are the vignettes of mutual dependence described in this editorial or in the symposium at all inclusive. An intimate interdependence between scientist and clinician utilizes fully Koch's principles that apply philosophical logic to science.

Objectivity about gains in medicine and science indicates what the public should have reinforced: that no single group deserves overwhelming accolades for the health benefits the people receive. Rather, it is the joint effort which merits praise. If success (to scientist, physician, patient and patron) is to be continued and consistent, the bonds of this interdependence must be defined and applied, and the results of this union must be demonstrable.

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Health Science and "Humanization"

THE SPECIAL ARTICLE by Professor Clark Kerr, formerly president of the University of California and now chairman of the Carnegie Committee on Higher Education, which appears elsewhere in this issue calls attention to what may be a most important role of medical and health science in the future of higher education in this nation. Dr. Kerr suggests that social changes which have already begun will profoundly influence higher education for many years to come. He notes that there is likely to be greater social emphasis on "humanization" with greater interest in a better access to a high quality of life for more people and with more attention being paid to the individual needs of people. In this connection he predicts "golden decades" ahead for the health sciences in terms of opportunities to do more and more for the American people. He stresses that the "health sciences are not only more central to the welfare of our people as a whole, but also more central to the conduct of higher education as our best contact with the people, our best service to the people." He goes further and says, "It may come to be that the greatest help that higher education will receive in this 'time of troubles' will be from the success of the health professions."

These are words to ponder for physicians and medical associations, as well as for medical educators. They suggest that the health professions will in the future, as is even now the case, be concerned with more than the prevention and cure of disease, although this will always remain a primary responsibility. In addition to this he is of the opinion that the health professions are destined to become inextricably involved in what may be called the "humanization" of human society and with it higher education. A concern with human individuality and the quality of human life is actually nothing new for physicians, who have always been more concerned with more aspects of human individuality than any other profession. And they have traditionally